1181-124 **Statin Promotes Coronary Collateral Circulation and Induces the Regression of Left Ventricular Mass in Patients With Angina**

Shin-ichiro Miura, Hiroaki Nishikawa, Masahiro Fujino, Bo Zhang, Hideki Shimomura, Hidekazu Arai, Akira Kawamura, Yoshihiro Tsuchiya, Kunihiro Matsuo, Keijiro Saku, Fukuoka University, Fukuoka, Japan, Fukuoka Tokusyukai Hospital, Fukuoka, Japan

Background: There is evidence that hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) promote collateral circulation (CC) in ischemic limbs and induce the regression of left ventricular mass (LVM) in animal models. Therefore, we investigated that the treatment with statin may associate with the development of coronary CC (CCC) as assessed by Rentrop Score (RS) or the regression of LVM index (LVMI) as assessed by echocardiography in patients with angina.
Methods: The subjects included 304 patients with angina who underwent coronary angiography. Study 1: Subjects who received pravastatin with one (1V), two (2V) or three (3V) significantly stenosed vessels were defined as cases (n=42), and age, sex and body mass index (BMI)-matched controls without statin treatment (n=100) were selected. Study 2: Those who received pravastatin or simvastatin were defined as cases (n=66), and age, sex and BMI-matched controls (n=127) were selected.
Results: Study 1: The cases included a higher percentage of 3V patients with RS>1 than the controls but there was no difference among 1V and 2V patients, suggesting that statin was associated with CCC independent of the number of stenosed vessels. Patients with 3V disease who were treated with statin were most likely (odds ratio:17.4(4.4-115)) to develop CCC, as assessed by a multiple logistic regression analysis. Study 2: The cases showed a significant decrease in LVMI (126g/m2) compared to the controls (148g/m2). Although the cases had a significantly higher percentage of patients with hypertension (HT) and calcium antagonist (CaA) treatment than the controls, there was no relationship between LVMI and HT or CaA treatment. Although the cases had significantly more stenosed vessels than the controls, there was a significant effect of interaction between LVMI with statin treatment and the number of stenosed vessels as assessed by ANCOVA.
Conclusions: Treatment with statin was associated with the existence of CCC and the regression of LVMI in patients with angina, suggesting that these effects may play a role in the pleiotropic effects of statin and may be beneficial in coronary heart disease.

1181-125 **Statins in General and Atorvastatin in Particular Do Not Affect Platelet Inhibition With Clopidogrel During Coronary Stenting**

Victor L. Serebruany, Alex I. Malinin, Steven R. Steinhubl, Kevin P. Callahan, Paul A. Gurbel, Sinai Hospital, Johns Hopkins University, Baltimore, MD

**Background:** Platelet activation following stent implantation is well documented and may affect both short- and long-term clinical outcomes. Clopidogrel is widely used to produce sustained platelet inhibition in order to prevent further ischemic events in patients with atherothrombosis. Certain clinical scenarios exist when treatment with clopidogrel is combined with the chronic use of statins. It has been recently reported that some statins, and atorvastatin in particular, may selectively interfere with clopidogrel, limiting the ability of this ADP-receptor blocker to inhibit platelet function.
**Methods:** We analyzed the data from the PRONTO (Plavix Reduction of New Thrombus Occurrence) trial, which evaluated platelet inhibition produced by loading dose clopidogrel pre- and post-stenting to determine whether the use of statins influence the ability of clopidogrel to inhibit platelets. Platelets were assessed by conventional plasma aggregometry induced by 5μM ADP and by expression of GP IIb/IIIa (CD41b), and PECAM-1 (CD31) by whole blood flow cytometry at baseline, at discharge, and at day 5 following stent implantation.
**Results:** Data from 100 patients were analyzed. Twenty-five patients were treated with a statin, (9 of those patients received atorvastatin) and 75 were not on statin therapy. Platelet inhibition by clopidogrel was identical in all groups, and resulted in 35-40% inhibition of aggregation, more than 50% reduction of GP IIb/IIIa expression, and 40-45% reduction of PECAM-1 expression at day 5 when compared with the baseline values. These effects were independent of statin use.
**Conclusion:** The study results suggest there are no apparent interactions between clopidogrel and statins.

ORAL CONTRIBUTIONS

## 856 Inflammatory Mediators of Atherosclerosis

Tuesday, April 01, 2003, 2:00 p.m.-3:30 p.m.
McCormick Place, Room S403

2:00 p.m.

856-1 **Reduced Endothelial Nitric Oxide Synthase Activity and Concentration in Umbilical Veins From Maternal Cigarette Smokers**

Malene R. Andersen, Line R. Walker, Steen Stender, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark

**Background.** The study aimed to investigate the effect of maternal cigarette smoking on endothelial nitric oxide synthase (eNOS) activity and concentration in the fetal umbilical vein, and to relate the findings to the size of the newborn.
**Methods.** Fourty-four nonsmoking and 30 smoking (average 15 cigarettes/day) women, living in a small area just north of Copenhagen, were included in the study. Umbilical vein endothelial cells were isolated immediately after delivery. The eNOS activity was determined in the samples by the conversion of $^{14}$C-L-arginine to $^{14}$C-L-citrulline, and the eNOS concentration by a human eNOS immunoassay.
**Results.** The two groups of women matched for sociodemographic and clinical characteristics. However, nonsmokers had a higher occupational status than smokers (Registrar General's social class 2.1+/-0.1 versus 2.8+/-0.1, $P$=0.001). Newborns of smokers had a lower weight (g 3398+/-64 versus 3649+/-58, $P$=0.014) and a smaller head circumference (cm 34.1+/-0.3 versus 35.1+/-0.2, $P$=0.002) than those of nonsmokers, but similar length and abdominal circumference. The eNOS activity in fetal umbilical veins exposed to intrauterine smoking was 40% lower (pmol L-citrulline/min/$10^6$ endothelial cells 27.1+/-2.2 versus 45.0+/-5.2, $P$=0.006), and the eNOS concentration 32% lower (ng eNOS/$10^6$ endothelial cells 1.7+/-0.2 versus 2.5+/-0.3, $P$=0.053) than in nonsmokers. The eNOS activity was associated with eNOS concentration ($r$=0.61, $P$<0.001) and the newborn weight ($r$=0.28, $P$=0.014). Multiple regression analysis showed that the reduction in eNOS activity associated with smoking was reduced by 40% when adjusting for eNOS concentration, and the reduction in birth weight by 26% when adjusting for eNOS activity.
**Conclusion.** The findings suggest that maternal smoking reduces nitric oxide production in the fetal circulation. This may contribute to retarded growth due to the subsequent endothelial dysfunction with reduction of dilatory capacity og the vessels.

2:15 p.m.

856-2 **Tumor Necrosis Factor-a Infusion Impairs Endothelial Function and Induces Endothelial and Metabolic Insulin Resistance in Humans**

Helena Domínguez, Christian Rask-Madsen, Nikolaj Ihlemann, Thomas Hermann, Lars Kober, Christian Torp-Pedersen, Gentofte University Hospital, Hellerup, Denmark, Joslin Diabetes Center, Harvard University, Boston, MA

**Background:** Tumor necrosis factor-alpha (TNF) levels are elevated in patients with acute coronary syndrome and in patients with type 2 diabetes. TNF impairs glucose uptake in animal models and in vitro. The aim of this study was to examine whether TNF infusion acutely impairs endothelial function and both insulin-stimulated endothelial function and glucose uptake in humans.
**Methods:** Lean healthy men were studied in the fasting state. Drugs were infused into the brachial artery measuring blood flow by venous occlusion plethysmography. Acetylcholine was used as endothelium-dependent agonist and nitroprusside as endothelium-independent agonist. Each study was based on three infusion series given the same day: infusing first the agonist alone, then co-infusing insulin and the agonist and finally co-infusing TNF, insulin and the agonist. For control, TNF and insulin were replaced by their vehicle in separate groups of volunteers. Glucose uptake was measured as the product between the arterial-venous difference of plasma glucose and forearm blood flow and expressed in uM [100 ml tissue]$^{-1}$ min$^{-1}$.
**Results:** There were performed 40 studies. During TNF infusion, local and systemic plasma TNF rose from 1.4 to 134±36 ng L$^{-1}$ in the perfused arm and to 6.5±1.4 ng L$^{-1}$ in systemic blood. The flow during maximal acetylcholine stimulation was 12.7±2.3 ml [100 ml tissue]$^{-1}$ min$^{-1}$. Insulin co-infusion enhanced this flow by 22% (p=0.0007). However when TNF was co-infused with insulin forearm decreased this flow by 32% to 8.6±2.3 (p=0.002) and TNF alone decreased it by 22% (p<0,0001). Insulin also enhanced forearm blood flow during nitroprusside infusion (p<0.001) and TNF blunted it (p<0.001). Insulin stimulated forearm glucose uptake by 1.0±0.1 (p=0.02) but this stimulation was completely blocked during TNF infusion since glucose uptake changed by −0.2±0.3 (p=0.5)
**Conclusion:** TNF infused in humans blunts endothelial function and both insulin-stimulated endothelium-dependent vasodilatation and glucose uptake.

2:30 p.m.

856-3 **Tumor Necrosis Factor-a Impairs Endothelium-Dependent Vasodilatation and Stimulates Local Tissue Plasminogen Activator Release in Humans: Diverse Vascular Actions of a Pleiotropic Cytokine**

Stanley Chia, Motaz Qadan, Richard Newton, Christopher A. Ludlam, Keith A. Fox, David E. Newby, University of Edinburgh, Edinburgh, United Kingdom, Royal Infirmary of Edinburgh, Edinburgh, United Kingdom

**Background:** Systemic and vascular inflammation contribute to the pathogenesis of cardiovascular disease, potentially through the actions of pro-inflammatory cytokines. The study aims were to assess the direct effects of local intra-arterial tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and endotoxin on blood flow and endogenous tissue plasminogen activator (t-PA) release *in vivo* in man. **Methods:** In a double-blind randomized placebo-controlled trial, blood flow, plasma cytokine and fibrinolytic factors concentrations were determined in both forearms of healthy male subjects using venous occlusion plethysmography and blood sampling. Ten subjects received intra-brachial infusions of TNF-α (80 or 240 ng/min), IL-6 (30 ng/min), endotoxin (100 pg/min) or saline placebo. Eight further subjects received intra-brachial infusion of bradykinin (0.1-1 nmol/min), acetylcholine (5-20 μg/min) and sodium nitroprusside (2-8 μg/min), two hours after pre-treatment with TNF-α (80 ng/min) or saline placebo. **Results:** Plasma TNF-α concentrations increased to 539±71 and 1164±41 pg/mL during TNF-α 80 ng and 240 ng infusion ($P$<0.001). TNF-α, but not IL-6, endotoxin or placebo, caused a slow onset and marked increase in plasma t-PA antigen and activity concentrations in the infused arm (21.1±3.8 ng/mL and 17.7±4.1 IU/mL, $P$<0.001) that was sustained for 4 hours. This occurred without an effect on blood flow but was associated with a rise in plasma IL-6 concentrations ($P$<0.05). Compared to placebo, TNF-α pre-treatment impaired endothelium-dependent